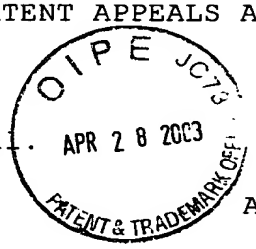
Atty. Docket No. 8012-1149

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES



In re application of

Nakayuki YAMAMOTO et al.

Serial No. 08/913,056 Appeal No. 2000-0317

Filed October 22, 1997 (GROUP 1617)

MUCOSAL PREPARATION CONTAINING PHYSIOLOGICALLY ACTIVE PEPTIDE

REQUEST FOR REINSTATEMENT OF APPEAL PURSUANT TO 37 CFR §1.193(b)(2)(ii)

MAY IT PLEASE YOUR HONORS:

Pursuant to the provisions of 37 CFR §1.193(b)(2)(ii), Appellants hereby request that the present appeal be reinstated. A Supplemental Brief is filed simultaneously herewith. That the conditions of 37 CFR §1.193(b)(2)(ii) are met in this case is evident from the discussion in the accompanying Supplemental Brief.

Respectfully submitted,

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April 28, 2003

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Nakayuki YAMAMOTO et al.

Serial No. 08/913,056 Appeal No. 2000-0317

Filed October 22, 1997 (GROUP 1617)

MUCOSAL PREPARATION CONTAINING PHYSIOLOGICALLY ACTIVE PEPTIDE

SUPPLEMENTAL APPEAL BRIEF PURSUANT TO 37 CFR §1.193(b)(2)(ii)

MAY IT PLEASE YOUR HONORS:

The present Supplemental Appeal Brief is filed pursuant to 37 CFR §1.193(b)(2)(ii), and in conjunction with the Request for Reinstatement of the present appeal filed simultaneously herewith, both in response to the recent reopening of prosecution by the Examiner after the appeal had previously been fully briefed. Although Rule 193(b)(2)(ii) refers to a "supplemental" brief, for the avoidance of confusion we note that the present brief addresses in full the issues now on appeal.

1. Real Parties in Interest

The real parties in interest in this application are the assignees, Asahi Kasei of Osaka, Japan, and Hisamitsu Seiyaku of Saga, Japan.

2. Related Appeals and Interferences

Appellants are unaware of any other appeal or interference which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

3. Status of Claims

Claims 1-27 are pending in this application, and the present appeal is taken from the final rejection of all of claims 1-27.

4. Status of Amendments

An Amendment after Final Rejection was filed May 11, 1999. There ensued an Advisory Action mailed June 4, 1999, which indicated that the Amendment after Final Rejection would be entered upon filing an appeal.

The appeal was fully briefed as of January 10, 2000, upon Appellants' filing of their Reply Brief. However, the case was remanded to the Examiner on June 15, 2001 (Paper No. 22) at

the request of the Group Director, to permit reconsideration of the issues on appeal. Despite a rather firm reminder in the Board's remand order that the case be dealt with promptly within the Group and that the Board be kept advised of its status, no further action was taken by the Group until November 26, 2002, when a new non-final action was issued, which sought to reformulate the rejection previously on appeal (the sole issue then on appeal) by the addition of six new secondary references to the seven references previously sought to be applied in combination, such that the three-component composition of the present claims is now rejected based on a proposed combination of thirteen references. Additionally, a subset of the claims on appeal were newly rejected based on a combination of three additional newly-cited references, and a further subset of the claims were rejected for the first time for indefiniteness, despite that the same claim language had been before the Examiner throughout the more than five year pendency of the application.

No amendment to the claims was made in response to the Official Action of November 26, 2002 (which amendment, if made, would have been pursuant to Rule 193(b)(2)(i)), Appellants instead opting under the circumstances for the approach outlined

in Rule 193(b)(2)(ii). Therefore, the claims on appeal are as amended by the amendment of May 11, 1999, and as shown in the accompanying appendix.

5. Summary of Invention

The invention is a pharmaceutical composition that allows greatly improved transmucosal administration of physiologically active peptides. The compositions of the invention have three principal components, namely (a) a physiologically active peptide such as insulin or calcitonin (the active ingredient), (b) an absorption promoter that promotes absorption of the physiologically active peptide by nasal or rectal mucosa and (c) a compound that has vasodilating activity without causing mucosal irritation (see, e.g., page 1, lines 6-9 of the present specification).

Conventionally, physiologically active peptides such as insulin and calcitonin are administered by injection, which is disadvantageous in that injections are painful, and not all patients are able to self-administer an injection (see page 1 of the specification).

Oral administration of physiologically active peptides is also unsatisfactory, because the active ingredient is

digested before it can be absorbed into the patient's bloodstream (see page 1, lines 20-23).

Numerous attempts have been made to formulate a physiologically active peptide with an absorption promoter, to permit transmucosal administration with satisfactory uptake of the drug, and a number of such prior art efforts are chronicled at pages 2-3 of the specification. However, none of the prior art formulations has been found to promote a satisfactory uptake of the active ingredient.

By contrast, the present inventors have discovered quite surprisingly that a three-component system as described above causes markedly increased absorption of the physiologically active peptide through the transmucosal administration route, by the combined use of an absorption promoter for transmucosal administration, together with a vasodilator that is a non-irritant on mucosal tissues (see the present Examples and Figures).

The present invention therefore contributes an important new administration composition for physiologically active peptides, whereby the peptides can be administered in satisfactory yield through a less invasive route, and one which is easier for patients to tolerate and self-administer.

6. Issues

By virtue of the Official Action of November 26, 2002, there are now several issues on appeal, as follows:

(1) Whether claims 1-27 would have been obvious, within the meaning of 35 USC §103(a), based on the collective teachings of the now thirteen references sought to be applied in combination, namely: MASIZ U.S Patent No. 5,645,854, ROBERTS et al. U.S. Patent No. 5,750,141, AZRIA et al. 5,149,537, KISSEL et al. ("Tolerability and Absorption Enhancement of Intranasally Administered Octreotide by Sodium Taurodihydrofusidate in Healthy Subjects", *Pharmaceutical Research,* Vol. 9, No.1, 1992, pp. 52-57), Japan 3-5427, EPA 215697, EPA 94157, COOPER U.S. Patent No. 4,557,934, EPA 115627, NAKAGAWA et al. U.S. Patent No. 4,882,359, MASADA et al. U.S. Patent No. 5,011,824, HANSEN et al. U.S. Patent No. 5,120,546 and MAJETI U.S. Patent No. 5,599,554;

(2) Whether claims 1-3, 18, 19 and 21-27 would have been obvious, within the meaning of 35 USC §103(a), based on the collective teachings of GYORY et al. U.S. Patent No. 5,240,995, SAGE, JR. et al. U.S. Patent No. 5,302,172 and HAAK et al. U.S. Patent No. 5,167,616, all first cited in the Official Action of November 26, 2002; and

(3) Whether claims 3-17 and 21 are sufficiently definite, within the meaning of 35 USC §112, second paragraph, in view of the grounds first stated in the Official Action of November 26, 2002, and despite that the language now objected to has been present in those claims since the filing of the present application on October 22, 1997.

7. Grouping of Claims

The claims are grouped separately for purposes of the present appeal, in that the Board's decision as to those newly-applied rejections that pertain to fewer than all of the pending claims will obviously have no impact on the other claims not subject to those rejections. With respect to the newfound indefiniteness rejection, claims 11 and 21 are rejected on grounds distinct from the perceived indefiniteness in claim 3, and hence are argued separately *infra*. With respect to each of the two prior art rejections on appeal, the claims are not grouped separately for purposes of this appeal, with the caveat that the rejection of claims 1-27 based on a proposed combination of thirteen references appears to be of the sort wherein certain references might be intended to apply only to certain claims; however the Examiner provides no roadmap as to

which references are considered pertinent to which claims, instead applying the references *en masse* and leaving it for the Board to sort out (to the extent that it can be sorted out, and to the extent that the Board is inclined to take on that burden); accordingly, if the Examiner were to attempt to fashion a more user-friendly form of that rejection belatedly by way of an Examiner's Answer, Appellants reserve the right to argue the claims separately at that time.

8. Argument

Issue 1

The primary reference to MASIZ is the only applied reference which discloses an active ingredient, a vasodilator and a permeation enhancer in combination; however, the delivery system of MASIZ is designed exclusively for transdermal administration, in contrast to the transmucosal formulation of the present invention, and the Examiner concedes that the primary reference fails to disclose or suggest the non-irritant vasodilators and transmucosal absorption promoters required by the present claims. For that purpose, the secondary references are relied upon, with ROBERTS et al. disclosing vasodilators including certain ones of those claimed for use in administering active ingredients other than physiologically active peptides as

claimed, and with the remaining five secondary references initially applied being essentially cumulative of the prior art discussed at pages 2-3 of the present specification, in that they describe compositions for transmucosal administration comprising an active ingredient and an absorption promoter, but which lack the required vasodilator.

Of the six newly applied secondary references, four (EPA 94157, EPA 115627, NAKAGAWA et al. and MASADA et al.) are in the same vein as those remaining five secondary references initially applied, in that they describe compositions for transmucosal administration comprising an active ingredient and an absorption promoter, but which lack the required vasodilator.

Newly-cited HANSEN et al. describes a multilamellar transdermal patch; however, contrary to the suggestion made at page 3 of the Official Action of November 26, 2002, alkyl-2-pyrrolidone permeation enhancers are not disclosed in combination with peptides such as insulin. Instead, the two substances are each listed separately among many other possibilities falling outside the scope of the claimed active ingredients and permeation enhancers, with no suggestion to use those particular two substances in combination, much less in further combination within the MASIZ "MULE" structure discussed

infra. Indeed, alkyl-2-pyrrolidone appears in a list of "potential" skin penetration enhancers whose use is optional in HANSEN and which are not necessarily even within the same layer of the HANSEN structure as the active ingredient (*c.f.* present claim 1, wherein the physiologically active peptide is admixed with the absorption promoter and non-irritant vasodilator).

Newly-cited MAJETI is said to teach that menthol is both a transdermal and transmucosal permeation enhancer. However, to the contrary, MAJETI merely lists menthol among a variety of other flavor components, to be added to its disclosed nicotine and caffeine delivery systems (neither of which ingredients is a peptide) in amounts of not more than about 1%, presumably when the composition is formulated as a gum for people trying to quit smoking (see Example 2 and its reference to a "buccal dosage form"; see also column 2, line 64, the reference to administration through the skin or oral mucosa).

Therefore, the propriety of the rejection on appeal turns on whether, absent the teaching of the present invention, the skilled artisan would have had the requisite motivation to replace the irritant vasodilators of MASIZ with suitable vasodilators for transmucosal administration such as those exemplified in ROBERTS for use with active ingredients other

than those claimed, and further to replace the transdermal permeation enhancers of MASIZ with any of the transmucosal absorption promoters of the remaining eleven secondary references.

However, a critical shortcoming of MASIZ for reference purposes relative to the claimed invention, is that the primary reference contemplates solely transdermal delivery of its active ingredient, and therefore not only fails to disclose or suggest the claimed vasodilators and absorption promoters suitable for transmucosal delivery, but also destroys any motivation to substitute components selected for use in one type of administration system, for use in an entirely different administration route. Moreover, the Examiner makes no attempt to carry his burden of showing why one skilled in the art would consider that the vasodilators of ROBERTS, used in conjunction with active ingredients other than physiologically active peptides, would be thought to confer any useful benefit to the MULE complex of MASIZ.

The Examiner disputes that the primary reference contemplates solely transdermal delivery, but there is no disclosure anywhere in the patent that discusses any other route of administration. The Examiner points to claim 16, and in

particular the mention of saliva, as an indication that transmucosal administration is "indicated".

However, a full consideration of the reference confirms that such a conclusion is inaccurate. In particular, column 5, lines 19-34 reveal that the MASIZ composition is in the form of a complex held together by a water-soluble gum. Saliva is disclosed solely in the context of a laundry list of body fluids having non-neutral pH, which serve to dissolve the gum to release the active ingredient. Therefore, this disclosure confirms that transmucosal delivery is in no way contemplated. That is, the complex must stay together through the route of administration, and only upon arrival at the intended destination should it release the active ingredient.

Moreover, the mention of saliva would not in any event suggest transmucosal administration, because although the mouth contains mucosal tissue, transmucosal administration of physiologically active peptides is effected through the nasal or rectal mucosal tissue. This is simply because, when a substance is placed in the mouth of a patient, the path of least resistance is ingestion and consequent digestion, not transmucosal absorption. As described at page 1, lines 20-23 of the present specification, oral administration is unsuitable for

the physiologically active peptides of the present invention.

The Examiner seems to recognize that, if appellants are correct in their assertion that the primary reference to MASIZ 5,645,854 teaches a composition contemplated solely for transdermal administration, then there could have been no motivation to replace the irritant vasodilators of the primary reference with suitable vasodilators for transmucosal administration such as those exemplified in the secondary reference to ROBERTS et al. 5,750,141, and further to replace the transdermal permeation enhancers of MASIZ with any of the transmucosal absorption promoters of the remaining eleven secondary references.

The Examiner's defense of the rejection on appeal is based on an effort to read MASIZ as teaching other than transdermal delivery of the disclosed composition. That effort plainly fails. The Examiner's position is based largely on the disclosure at column 5, lines 19-28 of the reference, and in particular on the laundry list of bodily fluids set forth at column 5, lines 25-28.

A fundamental flaw in the Examiner's analysis in this respect, however, is that the list of bodily fluids set forth at column 5, lines 25-28 of MASIZ simply bears no relation to the

delivery route of the disclosed composition, which the entire remainder of the reference emphatically describes as being solely transdermal. Instead, the bodily fluids at column 5, lines 25-28 of the reference are described as being those which release the active ingredient from the water soluble gum that binds the MASIZ composition together, to form the "MULE" complex described by the reference. The "MULE" complex is disclosed as being the transdermal transport vehicle, such that exposure to any member of the list of bodily fluids at column 5, lines 25-28 of the reference, serves to destroy the transport vehicle and render the composition unsuited for administration by any route. In other words, the list of bodily fluids at column 5, lines 25-28 of the reference come into play only after the MASIZ composition has been transported transdermally, which, again, is the sole route of administration contemplated by the reference.

The Examiner next argues that transmucosal administration is but an intended use of the claimed composition, and not given patentable weight. However, that position misses the point that the different administration routes of the secondary references militate against any proper combination with MASIZ as might otherwise result in the claimed composition, quite apart from the instant intended use. In the

same vein, the Examiner also seeks to dismiss the point that MASIZ fails to teach nasal or rectal delivery, noting that such delivery is not claimed. Again, the point is that the distinct delivery routes of the secondary references militate strongly against any proper combination of such references with MASIZ.

The Examiner also dismisses as "mere speculation" the point that the MASIZ "MULE" is unsuited for oral administration because the active ingredient "will be ingested [sic, digested] rather than absorbed." However, that point is well-supported in the present record: see page 1, lines 20-23 of the present specification, as noted above. See also page 1, lines 3-14 of EPA 94157. To the contrary, it appears that it is the Examiner's continuing effort to read MASIZ as teaching something other than transdermal delivery, which is lacking a factual basis in the present record.

The Examiner's reliance on the mention of mucoid secretions at column 5, line 25 of MASIZ likewise does nothing to improve the rejection, but rather underscores the impropriety of the rejection. Given that mucoid secretions are acknowledged by MASIZ as breaking down the transport vehicle described by the reference, it is clear that the compositions of the reference are unsuited for transmucosal administration, because by the

very terms of the reference, the transport vehicle would be destroyed before it had the opportunity to pass through such tissue.

The Examiner also argues that the vasodilator of MASIZ is not necessarily an irritant. Despite the "and/or" language in the abstract of the patent, however, all of the disclosed vasodilators of the reference are irritants, and a full reading of the reference indicates that the terms are used interchangeably. Indeed, the vasodilator of MASIZ is necessarily an irritant, to promote absorption of the active ingredients through the notoriously difficult transdermal route. Moreover, substances which are irritants on the skin will be all the more irritating to mucosal tissue, and unsuitable for use in the present invention.

Newly-cited MAJETI does nothing to dispel the above point, despite the characterization of the reference in the Official Action. As noted above, menthol in that reference is listed among a variety of flavorings, and used in minute concentrations when the nicotine/caffeine product is formulated as a gum. MAJETI is thus seen to have no relevance to MASIZ, as it is not at all apparent why one skilled in the art would wish to make a transdermal delivery system taste good.

From the above discussion, it is believed to be apparent that the addition of six newly-applied references to the previous combination of seven references, does not improve the quality of the rejection resulting from the attempted combination of the thirteen. Instead, for the reasons given above, it is believed that this ground of rejection must be reversed.

Issue 2

In the new ground of rejection based on GYORY et al. in view of SAGE, JR. et al. and HAAK et al., the Official Action relies upon GYORY et al. as a primary reference, despite that GYORY et al. relates solely to an adhesive composition for use with electrically powered iontophoretic delivery devices, and not to any particular (or even general) pharmaceutical composition. Apparently, the disclosure of GYORY et al. is considered relevant by the Examiner solely for the mention in the abstract that the adhesive of GYORY et al. can be used to adhere an electrode assembly of an iontophoretic delivery device "...to a body surface such as skin or a mucosal membrane." It is therefore apparent from the outset that GYORY et al. is to be used as a template for an unabashed hindsight reconstruction of the invention, or at least an attempt thereat.

SAGE, JR. teaches that, within the context of iontophoretic delivery, the vasodilator tolazoline enhances transdermal delivery of lidocaine. Lidocaine is of course not a peptide, although certain peptides are mentioned at column 6, lines 6-11, in the context of a vastly longer list of many other types of possible active ingredients. However, no mention of an absorption promoter having absorption promoting action for a physiologically active peptide on nasal mucosa or rectal mucosa, as is required by the present claims, appears in SAGE, JR. et al.

HAAK et al. relates to a discovery that iontophoretic delivery of drugs surprisingly occurs more readily when applied to intact back skin. The nature of the drug to be delivered is not pertinent to the HAAK et al. invention, although peptides are mentioned in the passage at column 6, lines 36-68, and the optional use of various permeation enhancers is mentioned at column 7, 3-12.

The proposed combination of these references in the Official Action of November 26, 2002 is incomprehensible. In particular, the Examiner contends that it would have been obvious "to add a vasodilator to the vehicle of SAGE, JR. et al…in view of GYORY et al.", despite that SAGE, JR. is the

reference cited to teach a vasodilator in the first place, and despite that, as noted above, GYORY et al. does not relate to the compositions to be used in combination with their disclosed adhesive. Indeed, it is not at all apparent how GYORY et al. figures into the rejection as formulated, if at all.

When the references are considered collectively with a view toward attempting to fathom what the Examiner might have meant to say, it is readily apparent that nothing in the references would have suggested the three component composition claimed herein. In particular, there is simply nothing in these references, when considered collectively, that would have suggested to the skilled artisan the combined use in admixture of (a) a physiologically active peptide, (b) an absorption promoter having absorption promoting action for the physiologically active peptide on nasal mucosa or rectal mucosa, and (c) a compound having vasodilating activity without mucosal irritation. Instead, it appears that the newfound attempt to reconstruct the claimed invention based on these newly-cited references is nothing more than an exercise in impermissible hindsight. Reversal of this ground of rejection is therefore respectfully requested.

Issue 3

The Official Action of November 26, 2002 concludes with a rejection of claims 3-17 and 21 for alleged indefiniteness, which, as noted above, is surprising in that the very claim language objected to has been present since this application was filed over five years ago.

With respect to claims 3-10 and 12-17, the sole basis for the newfound indefiniteness rejection is that the term "higher" in claim 3 is allegedly "subjective" and hence indefinite, in the absence of a recitation of a specific carbon number range. However, the term "higher" in claim 3 appears in the context of the phrase "higher fatty acid". In that context, the Examiner does not even allege, much less substantiate, that the phrase "higher fatty acid" would not have a reasonably precise meaning to those skilled in the art. As such, the rejection cannot be sustained.

The Board is moreover invited to take judicial notice of its own records on this point. A query to the USPTO full-text database at www.uspto.gov reveals that the identical phrase "higher fatty acid" or "higher fatty acids" appears in the claims of fully 1074 U.S. patents issued since 1976. This of course underscores the point that the phrase does indeed have a

reasonably clear meaning to those skilled in the art, although we note again that, in any event, it would have been the Examiner's burden to demonstrate that it does not. Furthermore, while each case must surely stand on its own facts, it is difficult to envision a rationale that would justify affirming the indefiniteness rejection on the basis of the present record, and hence in so doing necessarily also disparaging the validity of such a significant portion of the USPTO's work product.

Claim 11 was rejected not only on that basis, but also based on the phrase "polyoxyhethylene lauryl" (see page 6, line 3 from the bottom of the Official Action of November 26, 2002). In fact, no such phrase appears in the claim. If the Examiner intended to refer to the phrase polyoxyalkylene lauryl that actually appears in claim 11, it is likewise clear that no indefiniteness exists, because, in the context of the fuller phrase "polyoxyalkylene lauryl, polyoxyalkylene (24) cholesteryl ether" in claim 11, it is reasonably clear that the concluding noun "ether" relates back to each of the preceding terms "polyoxyalkylene lauryl" and "polyoxyalkylene (24) cholesteryl".

Lastly, with regard to the dependent claim 21, the term "usual" was considered to be vague. However, that term appears in the context of the fuller recitation that "the

compound having vasodilating activity is admixed with below 1/2 of minimum usual dose as an effective component of the said compound in the preparation for transmucosal administration." The use of the term "usual" in the context of the minimum conventional dose of an active ingredient is believed to be entirely appropriate in that instance, as the particular amount will vary based on the identity of the active ingredient and is thus not susceptible to meaningful quantification in the claim; and, furthermore, the Examiner has again not demonstrated wherein the usual minimum dose of physiologically active peptides is not known to those skilled in the art with reasonable precision.

It is therefore believed that none of the newfound criticisms of the original claim language merits affirmance of the indefiniteness rejection in any respect.

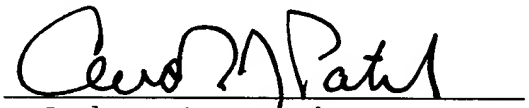
9. Conclusion

From the foregoing discussion, therefore, it is somewhat difficult to understand why the Group sought remand of this case two years ago, as the latest batch of rejections does not seem to bring forward anything more pertinent than was previously before the Board. In any event, it is believed to be

apparent that the rejection of claims 1-27 based on the proposed combination of MASIZ in view of the twelve secondary references, cannot properly be affirmed but instead must be reversed. Likewise, the new prior art rejection and the new indefiniteness rejection are believed to be improper for the reasons discussed above, and should be reversed. Such action is accordingly respectfully requested.

Respectfully submitted,

YOUNG & THOMPSON

By 

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April 28, 2003

10. Appendix

The claims on appeal:

1. A preparation for transmucosal administration comprising (a) a physiologically active peptide admixed with (b) an absorption promoter having absorption promoting action for the physiologically active peptide on nasal mucosa or rectal mucosa, and (c) a compound having vasodilating activity without mucosal irritation.

2. The preparation for transmucosal administration according to claim 1 wherein the absorption promoter having absorption promoting action for the physiologically active peptide on nasal mucosa or rectal mucosa has the absorption promoting action with improved absorption rate of above 200% on nasal mucosa or rectal mucosa as compared with a preparation without absorption promoter when insulin is used as the physiologically active peptide.

3. The preparation for transmucosal administration according to claim 1 wherein the absorption promoter is a member selected from the group consisting of salt of bile acid, salt of fusidic acid, salt of glycyrrhizic acid, salt of O-acyl-L-carnitine, phospholipid, non-ionic surface active agent, cyclodextrin, higher fatty acid, 1-alkyl-2-pyrrolidone derivative, 1-dodecylazacycloheptane-2-one, bacitracin, sodium zulenesulfonate, azacycloalkane derivative of the formulae

wherein R is an alkyl, m is an integer of 2 - 4 and n is an integer of 1 - 15, provided that R is an alkyl with a carbon number of 511 in case where n is 13, and mixtures thereof.

4. The preparation for transmucosal administration according to claim 3 wherein salt of bile acid is a member selected from the group consisting of sodium taurocholate, sodium glycocholate, sodium deoxycholate, and mixtures thereof.

5. The preparation for transmucosal administration according to claim 3 wherein salt of fusidic acid is a member selected from the group consisting of sodium fusidic acid, tauro-24, 25-dihydrofusidic acid, and a mixture thereof.

6. The preparation for transmucosal administration according to claim 3 wherein salt of glycyrrhizic acid is (member selected from the group consisting of salt of glycyrrhizic acid, disodium 3 -succinyloxyglycyrrhizic acid (carbenixolon), and a mixture thereof.

7. The preparation for transmucosal administration according to claim 3 wherein salt of O-acyl-L-carnitine is O-acyl-L-carnitine having Cs IS acyl.

8. The preparation for transmucosal administration according to claim 3 wherein salt of O-acyl-L-carnitine is a member selected from the group consisting of salt of O-octanoyl-

L-carnitine, salt of O-lauroyl-L-carnitine, salt of O-palmitoyl-L-carnitine, and mixtures thereof.

9. The preparation for transmucosal administration according to claim 3 wherein phospholipid is a member selected from the group consisting of phosphatidylcholine (lecithin), lisophosphatidylcholine (lysolecithin), lysophosphatidylglycerol, and mixtures thereof.

10. The preparation for transmucosal administration according to claim 3 wherein non-ionic surface active agent is a member selected from the group consisting of polyoxyalkylene higher alcohol ether, polyoxyalkylene alkylphenol, sucrose fatty acid ester, and mixtures thereof.

11. The preparation for transmucosal administration according to claim 3 wherein non-ionic surface active agent is a member selected from the group consisting of polyoxyalkylene lauryl, polyoxyalkylene (24) cholesteryl ether, and a mixture thereof.

12. The preparation for transmucosal administration according to claim 3 wherein cyclodextrin is a member selected from the group consisting of a-cyclodextrin, g-cyclodextrin, T-cyclodextrin, dimethyl g-cyclodextrin, and mixtures thereof.

13. The preparation for transmucosal administration

according to claim 3 wherein higher fatty acid is higher fatty acid of C16-20'

14. The preparation for transmucosal administration according to claim 13 wherein higher fatty acid of C16-20 is a C1S higher fatty acid selected from the group consisting of oleic acid, linoleic acid, linolenic acid, and mixtures thereof.

15. The preparation for transmucosal administration according to claim 3 wherein 1-alkyl-2-pyrrolidone derivative is C4-12 alkyl.

16. The preparation for transmucosal administration according to claim 15 wherein alkyl is a member selected from the group consisting of butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, and mixtures thereof.

17. The preparation for transmucosal administration according to claim 3 wherein azacycloalkane derivative of the formula (1) is azacycloalkane derivative in which R is C1O alkyl, m is 3 and n is 2.

18. The preparation for transmucosal administration according to claim 1 wherein the absorption promoter is admixed with 0.01 - 5 weight % of the said preparation.

19. The preparation for transmucosal administration according to claim 1 wherein the compound having vasodilating

activity is a member selected from the group consisting of calcium channel blocker of molecular weight 200 700, prostaglandin E1, isosorbide dinitrate, nitroglycerin, and mixtures thereof.

20. The preparation for transmucosal administration according to claim 19 wherein calcium channel blocker is a member selected from the group consisting of diltiazem hydrochloride, erapamil hydrochloride, bepridil hydrochloride, nifedipine hydrochloride, nicardipine hydrochloride, fasudil hydrochloride, and mixtures thereof.

21. The preparation for transmucosal administration according to claim 1 wherein the compound having vasodilating activity is admixed with below 1/2 of minimum usual dose as an effective component of the said compound in the preparation for transmucosal administration.

22. The preparation for transmucosal administration according to claim 1 wherein molecular weight of the physiologically active peptide is 300 - 10,000.

23. The preparation for transmucosal administration according to claim 1 wherein the physiologically active peptide is selected from the group consisting of insulin, calcitonin, human PTH (1-34), calcitonin gene related peptide (CGRP),

angiotensin II, vasopressin, desmopressin acetate, buserelin acetate, goserelin acetate, nafarelin acetate, leuprorelin acetate, somatostatin, glucagon, oxytocin, secretin, LH-RH, ACTH, TRH, TSH, ANP, derivatives containing synthetic or semisynthetic compound thereof, and mixtures thereof.

24. The preparation for transmucosal administration according to claim 23 wherein calcitonin is a compound selected from the group consisting of eel calcitonin, salmon calcitonin, porcine calcitonin, human calcitonin, chicken calcitonin, and mixtures thereof.

25. The preparation for transmucosal administration according to claim 24 wherein eel calcitonin is ASU1 7 eel calcitonin (elcatonin).

26. The preparation for transmucosal administration according to claim 23 wherein insulin is a compound selected from the group consisting of human insulin, porcine insulin, bovine insulin, and mixtures thereof.

27. The preparation for transmucosal administration according to claim 1 wherein the preparation for transmucosal administration is a preparation for administration in nasal mucosa, oral mucosa, pulmonary mucosa, rectal mucosa, vaginal mucosa or ocular mucosa.